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Anaplastic Large Cell Lymphoma: A Cytological Masquerade

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Abstract Anaplastic large cell lymphoma accounts for less than 10% cases of all lymphomas. It is a distinct category of large cell lymphomas that shows strong expression of CD30. The reproducibility of ALCL on the morphological ground is poor and at times it may mimic other non-lymphoid malignancies. The cytomorphology of anaplastic large cell lymphoma (ALCL) is distinctive yet variable. Till date only few cases have described the cytologic findings of ALCL. We here present a case of ALCL who presented to us with cervical lymphadenopathy and high grade fever.

Keywords: *anaplastic large cell lymphoma, Fine needle aspiration, CD 30, ALK*

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1. Introduction

Anaplastic large cell lymphoma, also called Ki-1 lymphoma, is a morphologically and immunologically distinct subset of non-hodgkin's lymphoma originally, which accounts for 2% to 8% of all lymphomas. [1] Two distinct clinical forms of primary ALCL are recognized: limited to the skin and systemic. [2] This disease is characterized by the proliferation of pleomorphic large neoplastic lymphoid cells, which strongly express the CD30 antigen (Ki-1 antigen), usually growing in a cohesive pattern and preferentially spreading in the lymph node sinuses and at times mimic other non lymphoid malignancies. [2,3] We hereby present a case of ALCL in a 35 year old patient whopresented with fever andcervical lymphadenopathy.

2. Case Presentation

A 35 year old man presented with swelling in left upper cervical region since one month, measuring about 2cm in diameter, non- tender, firm and immobile. On general examination patient was febrile, there was no other associated lymphadenopathy. Patient was farmer by occupation. On complete hemogram Hb- 8gm/dl, TLC-10000, DLC- P_{35} $L_{60}M_3E_2$, APC-2.5 lakhs. Montoux test was negative. There was no significant past and family history. Chest X-ray was unremarkable Fine needle aspiration (FNA) was done from the swelling using 23gauge needle. Both MGG and H&E staining were done. A blood mixed pus was aspirated. On microscopic examination, smears were highly cellular. The cells were mainly scattered singly, in sheets and arranged around capillaries with horseshoe-shaped nuclei, coarse chromatin, multiple 2-3 prominent nucleoli and abundant pale basophilic cytoplasm which was vacuolated at places. Numerous Bi-multinucleated cells with Reed-Sternberg–like appearance and mitotic figures were also seen in a background of lymphocytes, neutrophils, lymphoglandular bodies and RBCs. These anaplastic cells were large, at least 3 times the size of a resting lymphocyte nucleus.On Immunocytochemistry, cells were CD 30, ALK-1 and LCA positive. Hence, diagnosis of ALCL was made. Patient was given chemotherapy. Patient responded well to treatment, and is still on follow-up.

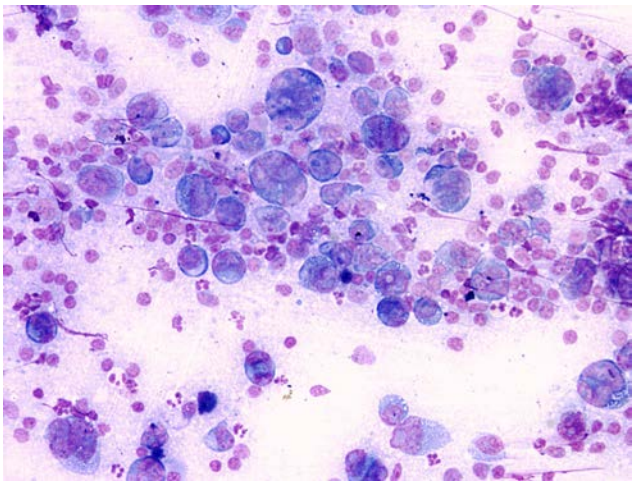

Figure 1. Atypical lymphoid cells mainly scattered singly with marked pleomorphic nuclei, coarse chromatin, 2-3 prominent nucleoli and abundant pale basophilic cytoplasm which is vacuolated at places (Giemsa 100x)

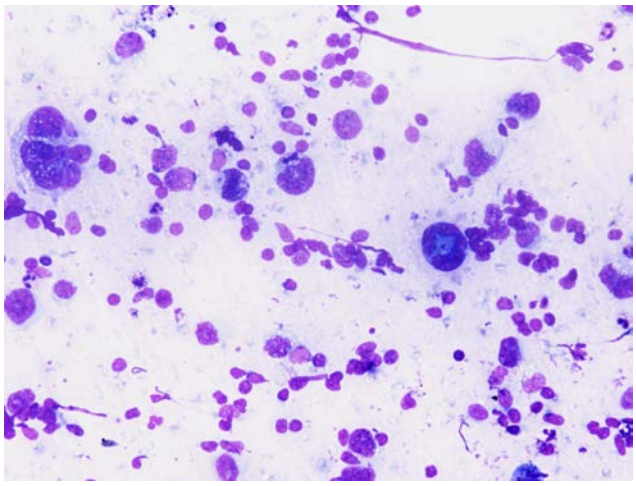

Figure 2. Numerous Bi-multinucleated cells with Reed-Sternberg–like appearance (Giemsa 200x)

3. Discussion

ALCL mostly occurs in the second and third decades of life with male/female ratio 6.5. This lymphoma frequently presents as an aggressive stage III to IV disease, usually associated with systemic symptoms (75%), especially high grade fever as in our case. Two distinct clinical forms of primary ALCL are now recognized: limited to the skin and systemic. The purely cutaneous ALCL may be indistinguishable from lymphomatoidpapulomatosis and regressing atypical histiocytosis as all may undergo spontaneous regression. [4] Conversely, systemic ALCL has an aggressive clinical course and patients frequently present with systemic symptoms, advanced-stage disease, and extranodal localizations.

It involves the lymph nodes and extranodal sites like skin, bone, soft tissue, lung, and liver. Mediastinal disease is less frequent. ALCL represents a distinct category of large cell lymphomas defined by a strong expression of CD30 on all or most of the neoplastic cells and a so-called anaplastic cytology, usually associated with a characteristic growth pattern of the tumor cells such as sinusoidal dissemination, and perifollicular or perivascular homing. The detection of CD30 (in conjunction with other lymphoid and non-lymphoid markers) is also important, not only in the differential diagnosis between ALCL and non-lymphoid anaplastic large cell tumors, but also to distinguish between ALCL and other types of lymphomas. It has recently been shown that the reproducibility of the diagnosis of ALCL on morphologic grounds is 46%, but it can be increased to 85% by immunostaining for CD30.

The diagnosis of ALCL by FNA requires the recognition of the diverse smear pattern. The anaplastic and pleomorphic cells can be lineage-nonspecific with very few clues for classification. Other than the varying clinical presentation, general dyscohesiveness of cells, moderate amphophilic cytoplasm, general lack of lymphoglandular bodies, it can be very difficult to pinpoint this entity as a lymphoma, let alone ALCL. [5] The hallmark cell is believed to be a clue and rather specific for the diagnosis of ALCL. The morphologic variants of ALCL delineated by the World Health Organization classification include monomorphic, lymphohistiocytic, small cell, mixed cell, giant cell and sarcomatoid types. [6] It appears that these variants do not have a prognostic implication. However, the ALK status of patients with ALCL may impart prognostic significance. ALK chimeric protein expression and the t(2,5) translocation can be found in 72% to 85% of ALCL cases. ALK-negative ALCL comprises the remaining cases and is observed to have a variable and unfavourable outcome [7].

The most discussed differential is Hodgkin lymphoma. In the common variant of ALK-positive ALCL, the number of anaplastic or hallmark cells are in the minority, similar to the pattern of RS cells noted in classic Hodgkin lymphoma. Both Hodgkin lymphoma and ALCL have neoplastic cells that stain for CD30 antibodies and have a mixed inflammatory background. Mourad et al found that FNA smears of ALCL had significantly more abnormal cells and multilobated cells than specimens of Hodgkin lymphoma. A high percentage of abnormal cells, a spectrum with regard to the size and type of pleomorphic or abnormal cells, and multilobated/wreath cells were findings that favored ALCL and not Hodgkin lymphoma. It is well known that Hodgkin lymphoma may contain granulomas and multinucleated RS cells; however, wreath-like multinucleated giant cells are rarely if ever noted, in contrast to ALCL. In fact, ALK-negative ALCL may be a separate entity that has yet to be fully defined [8].

Poorly differentiated carcinoma also shows many discrete large pleomorphic cells and may be confused with ALCL. However, the absence of lymphoglandular bodies and the hallmark cell may eliminate the possibility of ALCL. The strong presence of cytokeratin and epithelial membrane antigen in the tumor cells indicate the diagnosis of carcinoma over ALCL.

Other malignant diagnostic entities that enter the differential diagnosis, based on both morphologic and immunocytochemical grounds, include diffuse large B-cell lymphoma, embryonal carcinoma, melanoma, sarcoma, reactive lymphoid hyperplasia and metastatic carcinoma. [9] All these entities can stain positively for the CD30 antigen and have anaplastic morphology. Although seminoma may cytologically resemble ALCL, with dispersed single pleomorphic cells in a polymorphous lymphoid background, they are distinct immunocytochemical entities. Because seminoma should not stain for ALK or CD30, the admixed benign lymphocytes may stain for T-cell markers; therefore, caution should be used [10].

In our patient diagnosis was reached on the basis of morphological and Immunocytochemical characteristics. The presence of severe pleomorphism in the smears was found to be correlated with >5 anaplastic cells per 10 high-power fields. The nucleoli varied from a single prominent large nucleolus usually irregularly shaped, to multiple small nucleoli. Many such cells also contained clear, minute cytoplasmic vacuoles. The average mitotic count per 10 high-power fields was low.

4. Conclusion

The accurate diagnosis of ALCL has important clinical implications because it is a highly treatable form of lymphoma and has a much better prognosis than other types of T-cell lymphoma. Although difficult, ALCL can be accurately diagnosed by FNAC. The importance of

obtaining adequate material, keeping a wide differential diagnosis, and utilizing both immunochemistry and molecular techniques when one encounters an anaplastic neoplasm cannot be underestimated. [11] Careful cytological evaluation of hallmark cells and wreath-like multinucleated giant cells will provide a clue for further investigation, including the necessary staining for ALK or procuring material via FNA biopsy for cytogenetic studies [7]. CD30 status is no longer sufficient for a diagnosis of ALCL because the prognostic implications of ALK are significant.

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